



Biomarkers and Surrogate Endpoints

In the United States, people rely on the U.S. Food and Drug Administration to ensure that the drugs, biologics, or devices they use have acceptable risks and will help them feel or function better, or live longer. Clinical trials are conducted in order to demonstrate that new medical products deliver this positive balance of benefit and risk.

What are biomarkers?

Biomarkers, in layman's terms, are physical, biochemical, or genetic characteristics that are objectively measured and evaluated as indicators of health, disease, or a patient's response to a therapeutic intervention. Biomarkers can help diagnose a disease, or predict future disease severity or outcomes, like measurements of blood pressure as an indicator of heart health or measurements of blood sugar in diabetes. Biomarkers also are used to identify the best treatment for a patient, to monitor the safety of a therapy, or to find out if a treatment is having the desired effect on the body.

Many biomarkers used today have been developed to be used in a specific disease or as part of the development program for a specific medical product. Under the FDA's recently established Biomarkers Qualification Program, biomarkers shown to be useful indicators across different development programs may be designated by the FDA as qualified biomarkers.

What are endpoints when used in a clinical trial?

A clinical trial's "endpoints" are measurements of what happens

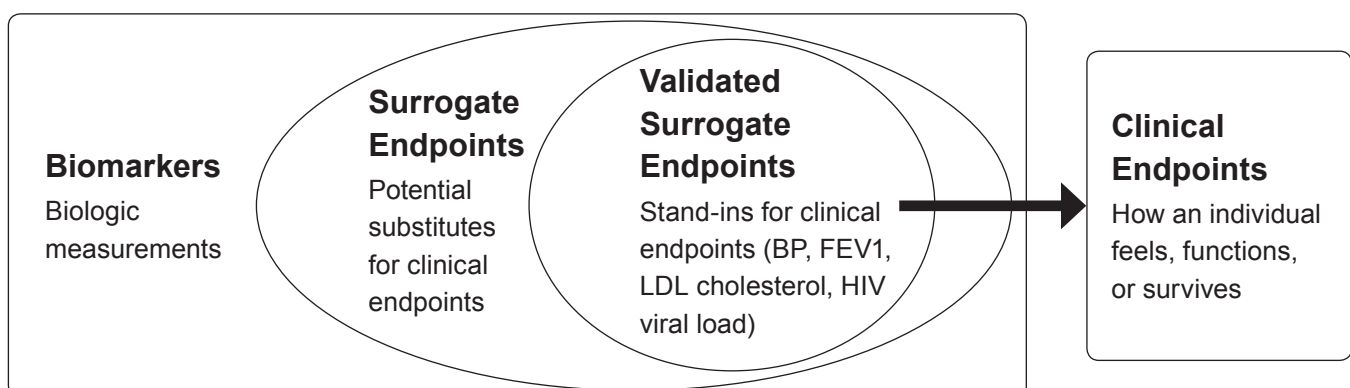
to people in the trial. When a trial is intended to evaluate a new medical product or a new use of an approved product, its endpoints usually measure benefit. Investigators typically use either clinical or surrogate endpoints.

Clinical endpoints are the most reliable clinical trial endpoints. They directly measure what matters most to people—whether they feel or function better, or live longer. Therapies can be recommended with confidence when clinical trials show that benefits, as measured by clinical endpoints, outweigh the adverse effects.

Surrogate endpoints are biomarkers that are used instead of clinical endpoints in some clinical trials. Surrogate endpoints are used when the clinical endpoints might take a very long time to study, or in cases where the clinical benefit of improving the surrogate endpoint, such as controlling blood pressure, is well understood. Clinical trials are needed to show that surrogate endpoints can be relied upon to predict, or correlate with, clinical benefit. Surrogate endpoints that have undergone this testing are called *accepted*, *established*, or *validated surrogate endpoints* and these are accepted by the FDA as proof of benefit. Between 2010 and 2012, the FDA approved 45 percent of new drugs on the basis of a surrogate endpoint.

How are biomarkers, clinical endpoints and surrogate endpoints related?

The relationships between these different endpoints is summarized in the graphic below.





What are examples of validated surrogate endpoints used in medical product development?

There are many examples of validated surrogate endpoints used in specific settings, including those below.

Validated Surrogate Endpoint	Correlated Clinical Endpoint
Systolic blood pressure (SBP)	Occurrence of stroke
Low density lipoprotein cholesterol (LDL) level	Occurrence of heart attack
Forced expiratory volume in 1 second (FEV1) <i>The amount of air that a person can blow out of his or her lungs in 1 second</i>	Improved breathing after taking medication for chronic lung diseases such as asthma
Human immunodeficiency virus (HIV) viral load <i>The amount of the human immunodeficiency virus that is present in the blood</i>	Development of an acquired immunodeficiency syndrome (AIDS) diagnosis

Importantly, even validated surrogate endpoints can give misleading information about the overall risk and benefits of a medical product. Some therapies that have demonstrated improvement using a validated surrogate endpoint in one setting have been shown to be ineffective or even harmful in another, usually because of additional effects that are not measured by the surrogate.

Are surrogate endpoints that have not been validated useful in medical product approvals?

Some surrogate endpoints may stand in for clinical endpoints when those surrogate endpoints are “reasonably likely to predict” clinical benefit, but not validated. This is accomplished under FDA’s Accelerated Approval program, which is intended to provide patients with serious diseases more rapid access to promising therapies. Because the surrogate endpoints used in the Accelerated Approval program have not been validated,

sponsors must verify the predicted clinical benefit of their products with post-approval clinical trials.

Why are biomarkers and surrogate endpoints important for medical product development?

When a surrogate endpoint is clearly shown to predict a beneficial effect through appropriate studies, its use generally allows clinical studies to be conducted in smaller numbers of people over shorter periods of time. For example, a sufficient number of clinical trials have demonstrated that reducing systolic blood pressure reduced the risk of stroke. Hence, measurement of reduction in the surrogate endpoint of systolic blood pressure can stand in for the clinical endpoint of stroke, and clinical trials targeting the reduction of risk of stroke can be conducted more rapidly in smaller populations using this surrogate.

What is the challenge of using biomarkers and surrogate endpoints in medical product development?

Biomarkers and surrogate endpoints alone do not give us the total picture of benefit and risk of a therapy. For example, surrogate endpoints may sometimes fail to predict the overall benefit and/or risk for a medical product. These limitations underscore the importance of continued evaluation in the post-market phase when products are approved based upon unvalidated surrogate endpoints, as well as the need to rigorously evaluate and sometimes re-evaluate surrogate endpoints clinically. Despite such caveats, as science and technology advance, it is hoped that the increased use of biomarkers and surrogate endpoints will facilitate the more efficient development of safe and effective medical products.

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